Remarks

Reconsideration of this Application is respectfully requested.

Claims 41, 52 and 54-63 are pending in the application, with claim 41 being the independent claim. Claims 50, 55, 59 and 63 have been amended by the present reply. Support for amended claims 50 and 63 can be found, *inter alia*, in the specification at p. 50, lines 22-30 and p. 52, lines 16-27, and in priority Appl. No. 08/159,184 at p. 19, lines 21-32. Support for amended claims 55 and 59 can be found, *inter alia*, in the specification at p. 42, lines 29-33, and in priority Appl. No. 08/159.184 at p. 26, lines 29-36. These changes introduce no new matter as they are fully supported by the specification as filed, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Nonstatutory Double Patenting Rejection

Claims 41, 50, 56, 57, 59, 61, and 62 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-11 of U.S. Patent No. 6,602,510. (Paper No. 200505, p.2.) Applicants respectfully traverse this rejection, but request that the rejection be held in abeyance until such time that the pending claims are found allowable.

Claims 41, 50, 56, 57, 59, 61, and 62 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-31 and 35-39 of copending Appl. No. 10/149,915. (Paper No. 200505, p.2.) Applicants

respectfully traverse this rejection, but request that the rejection be held in abeyance until such time that the pending claims are found allowable.

As noted in Applicants' Reply filed on February 10, 2005, according to § 804(I)(B) of the Manual of Patent Examining Procedure (M.P.E.P.), when provisional double patenting issues are raised in copending applications, "[i]f the 'provisional' double patenting rejections in both applications are the only rejections remaining in those applications, the examiner should then withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent. The examiner should maintain the double patenting rejection in the other application as a 'provisional' double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent."

Applicants will appropriately address the double patenting rejection in the event it is converted to an actual double patenting rejection pursuant to MPEP § 804(I)(B).

Objection to the Oath or Declaration

The Examiner has requested a new oath or declaration. (Paper No. 200505, p. 3.) Applicants file herewith a new oath or declaration. Applicants note that in accordance with 37 C.F.R. §§ 1.63 and 1.67, no claim for priority to U.S. applications is required to be set forth in an oath or declaration. The only requirement with respect to the listing of prior applications in an oath or declaration is the requirement to list foreign priority applications. 37 C.F.R. § 1.63(c)(2). Furthermore, the MPEP notes that a reference to a prior application can be inserted as the first sentence of the specification of the current application or in an Application Data Sheet (37 C.F.R. § 1.76) if applicant intends to rely

on the filing date of the prior application under 35 U.S.C. §§ 119(e) or 120. *See* MPEP § 201.11; *see also* 37 C.F.R. § 1.78(a). Applicants note that the current priority claim was inserted into the first sentence of the specification in a Preliminary Amendment filed February 11, 2004. Thus, the amendment to priority has been properly claimed. *See* 37 C.F.R. § 1.78(a). Accordingly, Applicants respectfully submit that the objection has been rendered moot.

Rejections under 35 U.S.C. § 103

Claims 41, 50, 56, 57, 59, 61, and 62 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Boon, U.S. Patent No. 5,342,774 ("Boon") in view of Rotzschke *et al.*, *Immunology Today*, *12*: 447-455 (1991) ("Rotzschke") and Rammensee *et al.*, WO 92/21033 ("Rammensee") as evidenced by Rammensee *et al.*, U.S. Patent No. 5,747,269, which corresponds to the U.S. national stage application of WO 92/21033. (Paper No. 200505, pp. 3-6.) Applicants respectfully traverse the rejection.

I. The Examiner has not established a prima facie case of obviousness.

The Examiner has alleged that the claims 41, 50, 56, 57, 59, 61, and 62 are unpatentable over Boon in view of Rotzschke and Rammensee. Applicants respectfully disagree.

In order to establish a *prima facie* case of obviousness, the following three criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when

combined) must teach or suggest all the claim limitations. MPEP § 2143. Furthermore, without a motivation to combine, a rejection based on a *prima facie* case of obviousness is improper. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Applicants assert that the prior art references when combined do not teach or suggest all of the claim limitations, nor do they provide a reasonable expectation of success. Furthermore, Applicants assert that there is no suggestion or motivation to combine the reference teachings, and thus the criteria necessary to establish a *prima facie* case of obviousness has not been met.

Applicants note that the currently pending claims are directed to the oligopeptide KVAELVHFL. As acknowledged by the Examiner's own statement, "Boon et al. do not teach the peptide KVAELVHFL." (Paper No. 200505 p.4) In addition, Boon does not provide any suggestion or motivation to make the specific peptide of the claimed invention.

Boon discloses that a class of antigens exist on the surface of tumor cells and that these antigens are referred to as tumor rejection antigens (TRAs). (Boon, col. 2, ll. 36-40.) Boon describes the precursor molecules of TRAs as tumor rejection antigen precursors (TRAPs). (Boon, col. 3, ll. 25-33.) Boon also describes the identification of one such family of TRAPs, the MAGE family. (*See e.g.* Boon, col. 19, ll. 35-63.)

The Examiner has alleged that "Boon et al. teach that MAGE-3 is a TRAP which encodes TRA (tumor rejection antigen) wherein it is desirable to elucidate the identity of the actual peptide recognized by the CTL." (Paper No. 200505, p. 4.) Boon, however, provides no guidance as to *how* CTL peptides should be identified or selected. Furthermore, Boon does not teach identification of CTL epitopes of any specific length.

Thus, Boon does not even provide an initial step which goes toward the identification of a MAGE-specific peptide. Finally, as noted above, Boon does not teach Applicants' claimed peptide.

Rammensee does not cure the deficiencies of Boon. Rammensee describes a method for the determination of a peptide motif. (Rammensee, col. 1, ll. 5-10 and col. 27, ll. 45-58.) Rammensee merely discusses the retrospective identification of an epitope, as opposed to Applicants' use of motifs for an initial prediction of a previously unidentified epitope. (*See e.g.* Rammensee, col. 1, ll. 37-53.) As noted in Applicants' previous Reply, the method disclosed by Rammensee involves the isolation of intact molecules bound to major histocompatability complex (MHC) molecules, separating the peptides from the MHC complexes, and sequencing the separated peptides, as claimed therein.

None of the peptides disclosed in Rammensee correspond to Applicants' claimed peptide sequence, KVAELVHFL. Rammensee provides neither a teaching, nor any motivation, to identify Applicants' claimed peptide KVAELVHFL. At best, Rammensee only discusses *an initial step* in identifying *potential* CTL peptides.

The Examiner has stated that "Rammensee et al. disclose that using a motif screening system that the identity of a tumor cell peptide reactive with CTL can be determined and that HLA 0205 binds a 9mer peptide with an anchor residue of L at position 9." (Paper No. 200505, p. 4.) Assuming, *arguendo*, that the Examiner's statement is true, Rammensee, as the Examiner notes, discloses a *method for screening*. As such, Rammensee at best only describes the initial step that one of ordinary skill in the art would consider using in an attempt to identify peptides which bind HLA

molecules. Rammensee does not provide any specific guidance or motivation to identify Applicants' specifically-claimed peptide KVAELVHFL.

Applicants note that their invention, as described in the specification, considers several factors other than the nature of the crucial anchor residues in identifying specific peptide epitopes. Specifically, the specification describes that "epitope selection encompassing identification of peptides capable of binding at high or intermediate affinity to multiple HLA molecules is preferably utilized, most preferably these epitopes bind at high or intermediate affinity to two or more allele-specific HLA molecules." (*See e.g.* Specification, p. 18, ll. 3-10.) Thus, the identification of potential candidate epitopes based on motif is a *first step*. Examples of subsequent steps include: 1) determination of binding affinity of a potential peptide epitope; and 2) cross-reactivity of potential peptide epitopes to two or more allele-specific HLA molecules. (*See* Specification, p. 45, ll. 7-31 and pp. 76-77.) These subsequent steps serve to identify those specific epitopes which would be useful for inclusion into a vaccine. (*See id.*)

As noted above, Rammensee at best teaches an initial step, but does not inform the skilled artisan of subsequent steps. Furthermore, Rammensee does not disclose Applicants' claimed peptide KVAELVHFL. Rammensee does not even refer to the MAGE antigen. Accordingly, Applicants assert that Boon, in view of Rammensee, does not render the claimed invention obvious.

Rotzschke does not cure the deficiencies of Boon or Rammensee. The Examiner states that Rotzschke discloses that peptide motifs can be used to scan protein sequences to identify T cell epitopes. (Paper No. 200505, p. 4.) Rotzschke describes that the analysis of naturally-processed peptides can yield information on the content of the

MHC groove and provide insights into the mechanisms of peptide generation and presentation. (Rotzsche, Abstract.) However, Rotzsche does not disclose Applicants' claimed peptide KVAELVHFL. Rotzsche likewise fails to disclose MAGE or any MAGE-specific peptides.

Moreover, Applicants assert that one skilled in the are would not have success in obtaining the claimed invention even if Boon were combined with Rammensee and/or Rotzsche. As described above, Applicants' invention is the result of *multiple selection criteria, of which motif identification is just one step.* (*See e.g.* Specification, p. 45, ll. 7-31 and pp. 76-77.) Applicants' claimed invention, in addition to motif identification, also relies on studies of peptide binding (*see e.g.* Specification, p. 168) and immunogenicity (*see e.g.* Specification, p. 172). Thus, the claimed invention cannot be obvious based on these references, either taken individually or in combination.

Statements made within the Rotzschke article further support the contention that Rotzschke is only a starting point and an invitation to experiment. For example, Rotzschke states that "*the consensus motif is merely a minimal requirement* if a peptide is to be selected for presentation on MHC molecules, and *it is likely that further conditions must be met.*" (Rotzschke, p. 450, col. 2 (emphasis added).) The Examiner has referred to the statement in Rotzschke that "allele-specific consensus motifs can be used to scan protein sequences to identify T cell epitopes." (Paper No. 200505, p. 5.) Applicants assert that the statement itself describes *an initial step* in the identification of a *potential* CTL epitope candidate peptide and that Rotzschke is merely an invitation to experiment.

An invitation to experiment or an "obvious-to-try" standard has been deemed as improper grounds for a § 103 rejection. *See e.g. In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988); *In re Fine*, 837 F.2d 1071, 1075 (Fed.Cir.1988); *In re Geiger*, 815 F.2d 686, 688, (Fed.Cir.1987). In view of the above, Applicants assert that a *prima facie* case of obviousness, with respect to claims 41, 50, 56, 57, 59, 61, and 62, has not been established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

II. Even assuming that a prima facie case of obviousness has been established, Applicants assert that this prima facie case of obviousness can be rebutted.

Assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicants assert that the *prima facie* case of obviousness can be rebutted. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *In re Dillon*, 919 F. 2d 688, 692-93 (Fed. Cir. 1990). Evidence of nonobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. MPEP § 716.02; *see In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987).

Applicants note that the data in Tables XXVI ("Crossbinding data A2 supermotif peptides") and XXVII ("Immunogenicity of A2 supermotif peptides") at pp. 176-177 of the specification shows that Applicants' claimed peptide KVAELVHFL exhibits a strong A2-supertype binding capacity. For example, the claimed peptide exhibits cross-reactivity with 5/5 A2 alleles tested, in addition to one of the strongest binding affinities with respect to the HLA alleles A*0202, A*0203, and A*6802 in comparison to other

peptides listed in Tables XXVI and XXVII. Specifically, the binding capacity of the claimed peptide KVAELVHFL for HLA A*0202 is 29 nM, for A*0203 is 14 nM and for HLA A*6802 is 17 nM. (*See* Specification, Table XXVI.) These binding capacity values are indicative of extremely strong binding affinities. (*See e.g.* Specification at p. 18, ll. 1-12 describing that a requisite binding affinity correlated with immunogenicity for HLA Class I has an IC_{50} value of 500 nM or less.) Thus, as shown above, the claimed peptide has a strong binding affinity and also cross-reacts with at least five HLA alleles. Thus, the binding characteristics of the KVAELVHFL peptide, as determined by Applicants, demonstrate that the KVAELVHFL peptide in fact has unexpected properties. Furthermore, as described above, the determination of binding affinity and cross-reactivity aids in the identification of epitopes which would be useful in a potential vaccine. (*See e.g.* Specification, p. 45, ll. 7-31 and pp. 76-77.) Thus, the characteristic that the claimed peptide would be useful in a vaccine provides a further advantageous property.

In view of the above, Applicants assert that this evidence of nonobvious or unexpected advantageous properties is sufficient to rebut a *prima facie* case of obviousness.

Accordingly, Applicants assert that even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness can be rebutted using the evidence described above. Thus, Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102

Claims 50, 56, 57, 59, 61, and 62 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Boon. (Paper No. 200505, p. 6.) Applicants respectfully disagree and traverse the rejection. However, solely in an effort to advance prosecution, Applicants have amended claims 50 and 59.

Amended claim 50 recites "[a] composition comprising the peptide of claim 41, wherein said peptide is linked to a spacer or linker, wherein said spacer or linker is between one and six amino acids in length." As noted above, Boon discloses a MAGE sequence which *comprises* Applicants' claimed peptide. Boon does not teach the exact peptide of Applicants' claimed invention. Furthermore, Boon does not teach a composition comprising Applicants' claimed peptide linked to a spacer or linker between one and six amino acids in length. Thus, Boon does not teach all of the limitations of claim 50. Accordingly, Boon does not anticipate amended claim 50.

Claims 56 and 57 depend from claim 41. Claim 41 recites "[a]n isolated peptide less than 15 amino acids in length comprising the oligopeptide KVAELVHFL (SEQ ID NO:711)." Claims 56 and 57 depend from claim 41, and therefore incorporate by reference all of the limitations of claim 41. *See* 35 U.S.C. § 112, fourth paragraph. As noted above, Boon discloses a MAGE sequence which *comprises* Applicants' claimed peptide. Boon does not teach the exact peptide of Applicants' claimed invention. Furthermore, Boon does not disclose a MAGE sequence 15 amino acids in length which comprises Applicants' claimed peptide KVAELVHFL. Thus, Boon does not teach all of the limitations of, and therefore does not anticipate, claims 56 and 57.

Amended claim 59 recites a composition comprising the peptide of claim 41, and one or more different *isolated* peptides, wherein said isolated peptide is a CTL inducing peptide or an HTL inducing peptide. As noted above, Boon merely discloses the native entire MAGE sequence which *comprises* Applicants' claimed peptide. Boon neither teaches the exact peptide of Applicants' claimed invention, nor does Boon teach a composition of Applicants' claimed peptide and one or more different isolated peptides, wherein the one or more different isolated peptides is a CTL inducing peptide or an HTL inducing peptide. Thus, Boon does not teach all of the limitations of claim 59. Claims 60 and 61 depend from claim 59, and therefore incorporate by reference all of the limitations of claim 59. *See* 35 U.S.C. § 112, fourth paragraph. As noted above, Boon does not anticipate claim 59. Thus, Boon does not anticipate claims 60 and 61, which depend from claim 59 and incorporate all of the limitations of claim 59.

Based on the above, Applicants assert that Boon does not teach all of the limitations of claims 50, 56, 57, 59, 61 and 62. Consequently, Boon does not anticipate these claims. As such, Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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